J Bioenerg Biomembr (2007) 39:31–34
DOI 10.1007/s10863-006-9056-8

MINI REVIEW

Chemotherapy through mitochondrial apoptosis using nutritional supplements and herbs: A brief overview

Kang-Beom Kwon · Byung-Hyun Park · Do-Gon Ryu

Published online: 16 February 2007

Abstract There has been increased interest in the use of naturally occurring compounds with chemopreventive and chemotherapeutic effects in the treatment of cancers. This review summarizes the most recent advances that provide new insights into the molecular mechanisms underlying the apoptotic potential of nutritional supplements and herbs. Apoptosis is an essential process in the pathogenesis of cancer and its mechanisms can be subdivided into either a death receptor-dependent extrinsic pathway or an independent (mitochondrial or intrinsic) pathway. Nutritional supplements and herbs can exert their effects on such pathways separately, sequentially, or in a manner of "crosstalk" between pathways. A strong correlation between the early collapse of the mitochondrial membrane potential and apoptosis was found for most nutritional supplements and herbs that have been studied. These observations provide examples of the development of mitochondrial targeting strategies for cancer therapy.

Keywords Mitochondria · Apoptosis · Herb · Nutritional supplement

Introduction

The mitochondria are energy and heat producing intracellular organelles that use oxygen for ATP production. Recent research, however, has shown that these organelles also play a key role in cell death when their membranes become permeable (Armstrong, 2006; Singh, 2006). Apoptosis is an active form of cell suicide controlled by a network of genes and is an essential process in cancer pathogenesis (Green and Kroemer, 2004; Green and Reed, 1998). Indeed, over the past decade, the molecular mechanisms driving apoptosis that are affected by anticancer treatments have provided the foundation for therapeutic strategies to combat cancer. Numerous novel approaches are currently being pursued and include gene therapy, antisense strategies, recombinant biology, irradiation, and anticancer drugs targeted to specific apoptotic regulators. One of the safest and more efficacious approaches is through the use of natural products or herbs.

In recent years, there has been growing interest in applying naturally occurring phytochemical-based compounds with anti-cancer potentials, because they are relatively non-toxic, inexpensive and available as oral forms. The herbs are typically prepared by steaming or heating crude plant materials, a method that has been used for centuries in Asia and Europe to manage the symptoms of cancer and even as a conventional treatment of cancer itself. Nevertheless, such practices are largely based on folklore and schools of traditional medicine rather than evidence-based research. We review herein the available scientific evidence related closely or directly to the bioactivity and potential health benefits of nutritional supplements and herbs that target cancer through mitochondrial pathway-dependent apoptosis. Information obtained from *in vitro* experiments reported in scientific literature is presented.

Discussion

Cancers are understood to arise from the disruption of the balance between cell growth and cell death. Defects in the execution of cell death may develop through alterations in

K.-B. Kwon · D.-G. Ryu (✉)
Department of Physiology, School of Oriental Medicine, Wonkwang University, Iksan 570-749, Jeonbuk, Korea
e-mail: tkryu@wonkwang.ac.kr

B.-H. Park (✉)
Department of Biochemistry, Medical School, and Institute for Healthcare Technology Development, Chonbuk National University, Jeonju 561-756, Jeonbuk, Korea
e-mail: bhpark@chonbuk.ac.kr

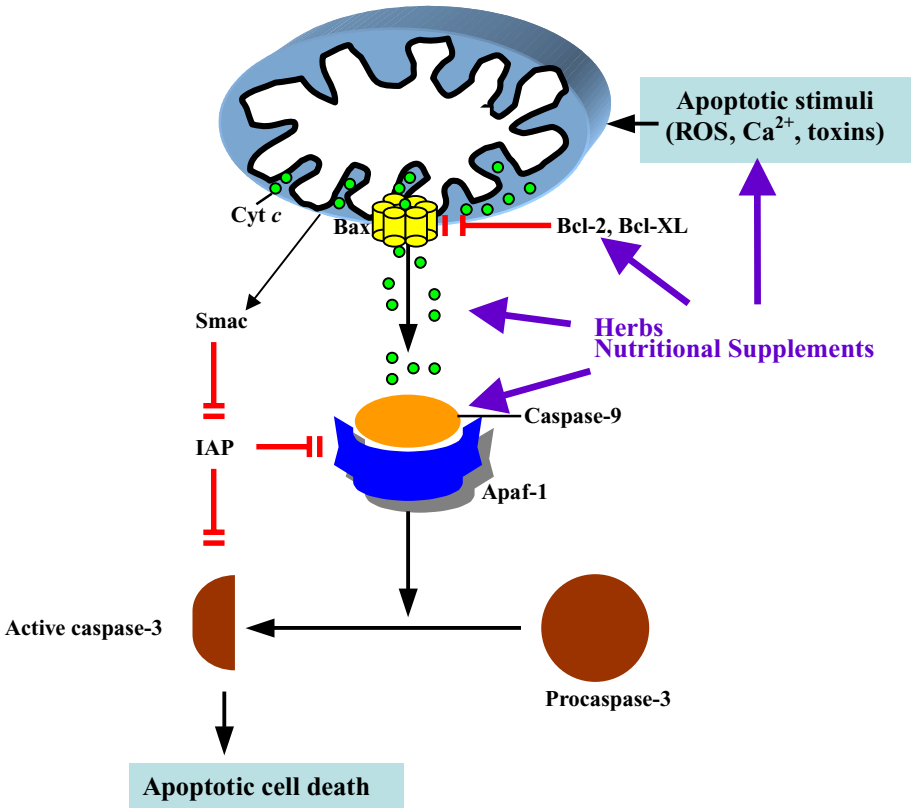

Fig. 1 Mitochondria-activated apoptosis model. Nutritional supplements and herbs trigger mitochondria to release Cyt *c* and initiate caspase-dependent apoptosis. Cyt *c* interacts with Apaf-1 to generate the apoptosome, a molecular platform for caspase-9 activation. Smac/DIABLO promotes caspase activation by neutralizing the inhibitory effects to the inhibitor of apoptosis protein (IAP). The catalytic maturation of caspase-9 activates caspase-3 and, ultimately, favors acquisition of the apoptotic morphology of cell death. The outer mitochondrial membrane permeability is regulated by the Bcl-2 family of proteins. Therefore, targeting strategies to induce apoptosis can be directed at either inhibiting Bcl-2 antiapoptotic proteins or inducing Bax-like proapoptotic proteins

the regulation of apoptosis. The induction of apoptosis in tumor cells, therefore, is a key mechanism open to study the effectiveness of preventive and therapeutic anticancer drugs (Brenner and Grimm, 2006; Kim, 2005). Evidence has accumulated to indicate that nutritional supplements and herbs induce apoptosis through numerous molecular targets in various apoptotic pathways. These components induce apoptosis through the activation of death receptors, the generation of reactive oxygen species (ROS), or the polarization of the mitochondria (Fresco et al., 2006; Martin, 2006).

Mitochondria are now recognized as regulators of apoptotic signaling as well as the energy powerhouses of cells. A variety of key events in apoptosis involve the mitochondria and include changes in electron transport, altered mitochondrial oxidation–reduction, a loss of mitochondrial membrane potential ($\Delta\psi_m$), and the release of cytochrome *c* (Cyt *c*). Dissipation of the electrochemical gradient is an early event and initiates the release of apoptogenic factors with subsequent Cyt *c* release as shown to occur in a variety of apoptotic models (Fig. 1). The inhibition of apoptosis by Bcl-2 or cyclosporine A may be mediated by blocking the release of Cyt *c* (Green and Reed, 1998; Kwon et al., 2001). It is of special interest that nutritional supplements and herbs known to alter mitochondrial membrane permeability and the release of Cyt *c* can induce apoptosis. The released Cyt *c* activates the caspases, a family of cysteine proteases, which are subdivided into initiators (caspase 8, 9, 10) and executioners (caspase 3, 6, 7). Once activated, a caspase cleaves many substrate proteins including poly (ADP-ribose) polymerase. It is for this reason that many strategies for cancer chemoprevention/chemotherapy are aimed at modulating and inhibiting caspase activities. Our studies have shown that *Radix Paeoniae Alba* and *Herba Houttuyniae* are effective at collapsing the mitochondrial membrane potential in HL-60 cells (Kwon et al., 2006; Kwon et al., 2003b). We have also demonstrated that Scorpio, the whole body of *Buthus martensii* K_{ARSCH}, inhibited HepG2 cell proliferation and caused cytotoxicity by inducing mitochondrial toxicity (Kwon et al., 2005). The nutritional supplements and other herbs reported to cause apoptotic cell death through a mitochondrial pathway are summarized in Table 1.

Mitochondria are a major source of ROS; mainly at the level of complexes I and III of the respiratory chain (Skulachev, 2006). The mitochondrial ROS might be responsible for oxidant-induced apoptosis. Thus, TNF-α, Fe^{2+}, and amyloid β-peptide-mediated apoptosis are blocked by overexpression of mitochondrial manganese superoxide dismutase which scavenges the superoxide that leaks from the mitochondrial respiratory chain (Dasgupta et al., 2006; Dhanasekaran et al., 2005; Keller et al., 1998). Other

Table 1 Induction of apoptosis by nutritional supplements and herbs through mitochondrial toxicity

	Sources	Cell model	References
ROS generation			
Takrisodokyeum	Mixture of 12 herbs	HL-60	Kwon et al. (2003a)
Diallyl disulfide	Garlic	HL-60,	Kwon et al. (2002)
		HCT-15	Park et al. (2002)
Scopoletin	Coumarin derivatives	HL-60,	Kim et al. (2005)
		PC-3	Liu et al. (2001)
Lectin-II	*Viscum coloratum* N_{AKAI}	U937	Kim et al. (2003)
Capsaicin	Chili peppers	Leukemia cells	Ito et al. (2004)
Cinnamaldehyde	*Cinnamomum cassia* P_{RESL}	HL-60	Ka et al. (2003)
Costunolide	Saussurea lappa C_{LARKE}	HL-60	Lee et al. (2001)
Eugenol	*Eugenia caryophyllata* T_{HUNB}	HL-60	Yoo et al. (2005)
Mitochondrial polarization			
Radix Paeoniae Alba	*Paeonia lactiflora* P_{ALLAS}	HL-60	Kwon et al. (2006)
Scorpio	*Buthus martensi* K_{ARSCH}	HepG2	Kwon et al. (2005)
Herba Houttuyniae	*Houttuynia cordata* T_{HUNB}	HL-60	Kwon et al. (2003b)
Rhein	*Rheum coreanum* N_{AKAI}	HL-60	Lin et al. (2003)
Lycopene	Tomato	LNCaP	Hantz et al. (2005)
Beta carotene	Orange-yellow vegetables	HL-60, HT-29	Palozza et al. (2003)
Curcumin	Turmeric, curry, mustard	HCT116	Rashmi et al. (2005)
Thymoquinone	*Nigella sativa* L_{INN}	HL-60	El-Mahdy et al. (2005)
Triptolide	*Tripterygium wilfordii* var. *regelii* M_{AKINO}	Leukemia cells	Carter et al. (2006)
Berberine	*Coptis chinensis* F_{RANCH}	HL-60, WEHI-3	Lin et al. (2006)
Chingwaysan	Mixture of 5 herbs	OC2, TSCCa	Liao et al. (2005)
Ent-11alpha-hydroxy-15-oxo-kaur-16-en-19-oic-acid (5F)	*Pteris inaequalis* var. *aequata* T_{AGAWA}	HT-29	Chen et al. (2004)

apoptotic stimuli, such as ceramide and glucose, elevate intracellular levels of ROS (Russell et al., 2002; Sawada et al., 2004). Antioxidants, such as *N*-acetylcysteine, suppress apoptosis by acting as scavengers for ROS and their actions provide further evidence that ROS act as signaling molecules to initiate apoptosis (Kwon et al., 2003a; Kwon et al., 2002; Park et al., 2002). Examples of the induction of apoptosis by nutritional supplements and herbs through the generation of ROS are presented in Table 1.

By their modulation of cell signaling pathways, nutritional supplements and herbs activate cell death signals and induce apoptosis in precancerous cells and malignant cells resulting in the inhibition of cancer development or progression. However, nutritional supplements and herbs must be used with caution. Few controlled research studies have actually evaluated their safety and efficacy (Basch et al., 2005; Messina, 2006). Herbs usually contain a range of pharmacologically active compounds and in some cases it is not known which of the constituents produces the therapeutic effect. Instead, the effect is often achieved by standardizing the amount of a single constituent of the extract. Because of the need for safety, guidelines for the dose and usage should be established. There has been an increase in the efforts to identify the biological mechanisms and in particular the mitochondrial pathway-dependent apoptotic pathway underlying the chemopreventive and therapeutic activities of nutritional supplements and herbs. An improved understanding of the molecular mechanisms of apoptosis involving the mitochondrial pathway will help to design more effective therapeutic regimens in anticancer-treatments.

Acknowledgements This work was supported by the Regional Research Center Program of the Korean Ministry of Education & Human Resources Development through the Center for Healthcare Technology Development.

Bibliography

Armstrong JS (2006) Br J Pharmacol 147:239–248
Basch EM, Servoss JC, Tedrow UB (2005) J Herb Pharmacother 5:3–15
Brenner C, Grimm S (2006) Oncogene 25:4744–4756
Carter BZ, Mak DH, Schober WD, McQueen T, Harris D, Estrov Z, Evans RL, Andreeff M (2006) Blood 108:630–637
Chen GG, Liang NC, Lee JF, Chan UP, Wang SH, Leung BC, Leung KL (2004) Apoptosis 9:619–627
Dasgupta J, Subbaram S, Connor KM, Rodriguez AM, Tirosh O, Beckman JS, Jourd'Heuil D, Melendez JA (2006) Antioxid Redox Signal 8:1295–1305
Dhanasekaran A, Kotamraju S, Karunakaran C, Kalivendi SV, Thomas S, Joseph J, Kalyanaraman B (2005) Free Radic Biol Med 39:567–583

El-Mahdy MA, Zhu Q, Wang QE, Wani G, Wani AA (2005) Int J Cancer 117:409–417
Fresco P, Borges F, Diniz C, Marques MP (2006) Med Res Rev, in press
Green DR, Kroemer G (2004) Science 305:626–629
Green DR, Reed JC (1998) Science 281:1309–1312
Hantz HL, Young LF, Martin KR (2005) Exp Biol Med (Maywood) 230:171–179
Ito K, Nakazato T, Yamato K, Miyakawa Y, Yamada T, Hozumi N, Segawa K, Ikeda Y, Kizaki M (2004) Cancer Res 64:1071–1078
Ka H, Park HJ, Jung HJ, Choi JW, Cho KS, Ha J, Lee KT (2003) Cancer Lett 196:143–152
Keller JN, Kindy MS, Holtsberg FW, St Clair DK, Yen HC, Germeyer A, Steiner SM, Bruce-Keller AJ, Hutchins JB, Mattson MP (1998) J Neurosci 18:687–697
Kim EK, Kwon KB, Shin BC, Seo EA, Lee YR, Kim JS, Park JW, Park BH, Ryu DG (2005) Life Sci 77:824–836
Kim MS, Lee J, Lee KM, Yang SH, Choi S, Chung SY, Kim TY, Jeong WH, Park R (2003) Life Sci 73:1231–1243
Kim R (2005) Cancer 103:1551–1560
Kwon KB, Kim EK, Han MJ, Shin BC, Park YK, Kim KS, Lee YR, Park JW, Park BH, Ryu DG (2006) Biol Pharm Bull 29:1082–1086
Kwon KB, Kim EK, Lim JG, Jeong ES, Shin BC, Jeon YS, Kim KS, Seo EA, Ryu DG (2005) World J Gastroenterol 11:943–947
Kwon KB, Kim EK, Shin BC, Seo EA, Park JW, Kim JS, Park BH, Ryu DG (2003a) Life Sci 73:1895–1906
Kwon KB, Kim EK, Shin BC, Seo EA, Yang JY, Ryu DG (2003b) Exp Mol Med 35:91–97
Kwon KB, Yang JY, Ryu DG, Rho HW, Kim JS, Park JW, Kim HR, Park BH (2001) J Biol Chem 276:47518–47523
Kwon KB, Yoo SJ, Ryu DG, Yang JY, Rho HW, Kim JS, Park JW, Kim HR, Park BH (2002) Biochem Pharmacol 63:41–47
Lee MG, Lee KT, Chi SG, Park JH (2001) Biol Pharm Bull 24:303–306
Liao PH, Chen SL, Shih HC, Chou MY (2005) Am J Chin Med 33:21–27
Lin CC, Kao ST, Chen GW, Ho HC, Chung JG (2006) Anticancer Res 26:227–242
Lin S, Fujii M, Hou DX (2003) Arch Biochem Biophys 418:99–107
Liu XL, Zhang L, Fu XL, Chen K, Qian BC (2001) Acta Pharmacol Sin 22:929–933
Martin KR (2006) Exp Biol Med (Maywood) 231:117–129
Messina BA (2006) J Perianesth Nurs 21:268–278
Palozza P, Serini S, Torsello A, Di Nicuolo F, Maggiano N, Ranelletti FO, Wolf FI, Calviello G (2003) Nutr Cancer 47:76–87
Park EK, Kwon KB, Park KI, Park BH, Jhee EC (2002) Exp Mol Med 34:250–257
Rashmi R, Kumar S, Karunagaran D (2005) Carcinogenesis 26:713–723
Russell JW, Golovoy D, Vincent AM, Mahendru P, Olzmann JA, Mentzer A, Feldman EL (2002) Faseb J 16:1738–1748
Sawada M, Kiyono T, Nakashima S, Shinoda J, Naganawa T, Hara S, Iwama T, Sakai N (2004) Cell Death Differ 11:997–1008
Singh KK (2006) Ann N Y Acad Sci 1067:182–190
Skulachev VP (2006) Apoptosis 11:473–485
Yoo CB, Han KT, Cho KS, Ha J, Park HJ, Nam JH, Kil UH, Lee KT (2005) Cancer Lett 225:41–52